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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,791	01/08/2005	Alexander Domling	62660(52171)	3248

21874 7590 02/19/2009

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
02/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,791	DOMLING ET AL.	
	Examiner	Art Unit	
	SATYANARAYANA R. GUDIBANDE	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-10 and 12-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10 and 12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/08 has been entered.

Election/Restrictions

Applicant's election without traverse of species as compound recited in claim 14 and 17, and addition of claims 14-17 in the reply filed on December 2, 2005 was acknowledged in the non-final office action dated 1/23/06.

Specification

The instant specification fails to conform to the order in which the different sections of the specification should be arranged as provided in 37 CFR 1.77(b). The specification lacks the sections under the following different sub-headings (b)-(i) as shown below.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Office acknowledges receipt of foreign priority papers submitted under 35 U.S.C. 119(a)-(d), which have been placed of record in the file.

However, applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(a)-(d), as follows:

a) Cross reference to related applications is missing in the specification of instant application.

b) Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

In the instant application, copy of the GERMANY 102 30 875.6 07/09/2002 and GERMANY 103 05 531.2 02/11/2003 documents are not in English. Hence priority will not be awarded beyond 7/9/03 the filing date of PCT/EP03/07415 07/09/03.

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Response to Amendments

Applicant's amendment to claim 7 in the response filed on 12/1/08 has been acknowledged.

Claims 7-10 and 12-22 are pending.

Claims 7-10 and 12-22 are examined on the merit.

Any objections and/or rejections made in the office action dated 10/29/07 and not specifically discussed below in original or modified form here are considered withdrawn.

Withdrawn Rejections

Claim Rejections - 35 USC § 112 (Enablement)

Applicant's arguments, see page 7, filed 12/1/08, with respect to rejection of claims 12, 13 and 16-19 have been fully considered and are persuasive. The enablement rejection had been made on 'how to make and use' the instant invention. The newly found prior art DE 10008089 A1 issued to Hoefle describes synthesis of tubulysin compounds produced by multi-stage process using known new starting materials and intermediates. The tubulysin compounds are known to

have been cytotoxic and hence have been used in the treatment of cancer. Hence the rejection has been withdrawn further in view of the newly found prior art.

Claim Rejections - 35 USC § 103

Applicant's arguments, see pages 5 and 6, filed 12/1/08, with respect to the rejection(s) of claim(s) 7-10, 14, 15 and 20-22 under 35 USC § 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of newly found prior art.

Maintained Rejections

Claim Rejections - 35 USC § 112

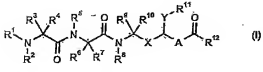
The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 10 and 12 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The rejection has been modified to reflect the amendments made to claim 7 and further concentrate on the issues in the claims that lack written description. Response to applicant's remarks at the end of the rejection.

The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant application, applicants claim a compound of general formula U-V-W wherein 'U' refers to formula I as shown below,



(I)

wherein

A is an optionally substituted 5- membered heteroarylen ring;

X is a group of the formula $CR^{14}R^{15}$;

Y is an oxygen atom,

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} R^{12}, R^{13}-R^{14}, R^{15} and R^{16} are independently of each other H, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteroaralkyl,

or two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, and R^{15} constitute part of a cycloalkyl or heterocycloalkyl ring system;

V is a linker and W is a polymer.

Applicants also claim a method of treating a patient suffering from cancer comprising administering to the patient one or more compounds instant claim 7.

The claims as recited in claim 7 represent innumerable compounds conjugated to a polymer in general with a linker of unknown chemical composition. The claims as recited and disclosure in the specification are inadequate to describe the claimed invention of the instant application in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing include:

a. Actual reduction to practice;
b. Disclosure of drawings or structural chemical formulas;
c. Sufficient relevant identifying characteristics such as:
    i. Complete structure,
    ii. Partial structure,
    iii. Physical and/or chemical properties or

iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure;
d. Method of making the claimed invention;
e. Level of skill and knowledge in the art and
f. Predictability in the art.

While all of these factors are considered, a sufficient number for a *prima facie* case are discussed below.

In the instant application, claims are drawn to a compound of general formula U-V-W, wherein the 'U' represents innumerable compounds of formula I as shown above, 'V' represents a linker moiety and 'W' is a polymer. Formula I represents a partial structure of the compound U-V-W. The various variables R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, and R^{15} as recited in the claim define a formula I and encompasses a large number of compounds of complex structural features. Because, as recited in the claim 7, any two of the above mentioned R variables constitute a part of a cycloalkyl or hetero-cycloalkyl ring system. This definition of the formula I imply that if R^1 and R^{12} (the two extreme ends of the molecule) form a cyclic ring, resulting in a 13 membered heterocyclic ring structure. However, the instant specification provides only three examples of polyethylene glycol (PEG) conjugates of tubulysin A molecule (pages 11-12) and examples of six tubulysin molecules as shown on page 1 of instant specification. There are no cyclic structures corresponding to formula I with a 13 membered heterocyclic ring have been disclosed in the instant specification. The only heterocyclic rings present in the elected species of tubulysin are the 5-membered thiozolyl and 6-membered hetero-cyclohexyl ring with 'N' as the heteroatom.

Claim 7 also recites the variable $\mathbf{R^{16}}$ that is neither defined nor present in formula I.

Formula U comprises the variable 'A' which is a 5 membered optionally substituted heteroaryl ring. Claim as recited does not define the chemical nature of the 5-membered ring

system in terms of type of heteroatoms, number of heteroatoms present or the optional substitutions on the ring. The specification discloses that the number of heteroatoms in the ring can be 1-4 and the heteroatoms are selected from O, N, S or P (page 5, paragraph 2). The only heterocycle shown in the elected species tubulysin is a thiozolyl ring system.

The claim as recited is a conjugate of moiety 'U' with a polymer 'W' using a linker 'V'. The claim 7, as recited does not provide any description as to nature of the linkers in terms of their chemical composition. The claim also does not identify the nature of the polymer conjugated to the moiety 'U' via the linker 'V'. Moreover, the claim as recited does not provide any structural disclosure to which portion or to which functional group of the moiety 'U' is used in the conjugation process. Claims 9 and 10 identifies the polymer as PEG but they fail to identify the point of attachment to the moiety 'U' and the chemistry involved in such conjugation. Also, claim 10 recites that the molecular weight of PEG more than 30 kDa with no upper limit set for the molecular weight of the polymer.

The specification is inadequate with respect to chemical synthesis any one of the compounds represented by moiety 'U'. It only provides support to the conjugate formation of tubulysin A (source of which is isolated from natural source as disclosed on page 1, paragraph 1 of instant specification) with PEG using known methods.

As aforementioned, the specification lists six tubulysin compounds on page 1 as representatives of 'U', and on page 7 linkers and polymers are disclosed as a list of compounds and on page 10 list of applications for the compounds, i.e., applicants' lists therapeutic uses for the compounds of instant invention. The disclosure also embodies only three structural variants of tubulysin compounds conjugated to PEG on pages 11 and 12. As per the requirement of the

written description criteria, the claims as recited and the disclosure in the specification is inadequate to describe the present invention that claims myriads of compounds of formula 1 along with variety of linker moieties conjugated to polymers. The specification is inadequate in describing how innumerable compounds represented by formula I are synthesized. The specification is silent on chemical synthesis of any of the number of variants of 'U' represented by formula I. In the absence of a synthetic scheme to make these compounds, the specification is also inadequate in describing the microbial source for isolating variety of structurally distinct myriads of compounds as represented by formula I. The specification is inadequate with respect to written description requirement in disclosing structure-function relationship of the compounds represented by formula I with representative number of examples commensurate with the scope of the claim. The specification is silent on how these compounds are screened for the desired biological activity of treating cancer. Specification provides a list of disease conditions where the instant invention can be used to treat including cancer (page 10, last paragraph).

The specification is vastly inadequate in describing the application of the compounds of instant invention in methods of treating cancer as claimed by the applicants. The specification lacks examples showing efficacy of any compound of innumerable compounds claimed in the instant invention in *in vitro* or *in vivo* studies, let alone treating patients suffering from cancer.

Therefore, the claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Arguments

Applicants argue that the claims as presented fully satisfy the written description, 'for instance the originally presented (specification) provide written description of the instant claims'.

Applicant's arguments filed 12/01/08 have been fully considered but they are not persuasive. Applicants have not provided any arguments pointing out disagreements with the examiner's contentions. Applicant must also discuss the references applied against the claims, explaining how the claims avoid the references or distinguish from them. Rejection as set forth above illustrates how the instant specification is inadequate in supporting the invention as claimed commensurate with the scope of the instant claims.

New grounds of Rejections/Objections

Claim Objections

1. Claim 7 is objected to because of the following informalities:

In the definition of the variable 'A', the claim recites the term "heteroarylen". The term should be "heteroaryl".

Further in describing variable R^1 to R^{16}, the claim recites the term 'heteraaralkyl". The term should read "heteroaralkyl".

2. Claims 16 and 19 are objected to because of the following informalities:

In the definition of the variable 'V', the claim recites "-O-(CR^aR^b)h-O-". The term should be "-O-$(CR^aR^b)_n$-O-".

3. Claims 16 and 20 are objected to because of the following informalities:

In the definition of the variable 'V', the claim recites "-NH-R^{e}-NH-CO-CH2-O-". The term should be "-NH-R^{e}, -NH-CO-CH2-O-".

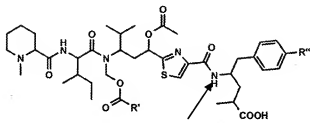
Appropriate corrections are required.

4. Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 12 recites a method of treating a patient suffering from cancer comprising administering to the patient one or more compounds of the invention. Claim 13 recites as identifying the patient as suffering from cancer. Being a dependent claim, claim 13 does not further limit the invention recited in the base claim, i.e., claim 12 from which it depends.

5. Claims 8, 12 and 14-19 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, i.e., claim 7. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 7 recites a formula I wherein various variables R^{1}, R^{2}, R^{3}, R^{4}, R^{5}, R^{6}, R^{7}, R^{8}, R^{9}, R^{10}, R^{11}, **R^{12}**, R^{14}, and R^{15} are defined as independently of each other H, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteroaralkyl. **R^{12}** is attached to the terminal carbonyl (CO) on the

right side of the formula I. The definition of $\mathbf{R^{12}}$ does not include substituents such as **-NR'R"** (moiety introduced by the office for description purposes only) wherein R' and R" can be independently H or moieties as shown in the structure for the tubulysin (as shown below, see the arrow in the figure). Hence the species of claims 8, 12 and 14-19 do not read on the formula I.



Therefore, the claims 8, 12 and 14-19 do not further limit the invention of the base claim 7 from which they depend from.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recite a limitation "R^{16}" as a variable. The currently amended claim does not have a variable "R^{16}" in the formula (I). Therefore, the presence of the variable "R^{16}" renders the claim vague and indefinite.

2. Claims 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recite "Method of claim 7" in the preamble. However, the claim 7 is drawn to "A compound". There is insufficient antecedent basis for this limitation in the claim.

Claims 21 and 22 recite "Method of claim 9" in the preamble. However, the claim 9 is drawn to "A compound". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102(a)/(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

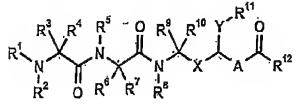
> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 7 and 8 are rejected under 35 U.S.C. 102(a/e) as being anticipated by Leung (US 2002/0169125 A1).

Leung anticipates the instant invention under 102(a) as priority is being denied for lack of English translation of the foreign priority documents in the file. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Leung anticipates the instant invention under 102(e) because the filing date (March 20, 2002) of Leung precedes the instant application.

In the instant application, applicants claim a compound of general formula U-V-W wherein 'U' refers to formula I as shown below,



(I)

wherein V is a linker and W is a polymer.

The formula 1 of the instant claim 7, reads on the elected species 'tubulysin'. Claim 7 as recited imply a compound of formula U-V-W wherein the formula I representing the moiety 'U' (tubulysin) conjugated to a polymer in general using a linker of unknown chemical structural characteristics.

Leung discloses a polyanionic polymer conjugated to a drug. The drug being selected from the group that consisted of tubulysin, dolastatin (psuedopeptides) which exhibits cytotoxic properties ([0012] and claim 45). Leung also discloses that the drug can be conjugated to the polyanionic polymer through an indirect linkage (linker) such as a bifunctional spacer [0051] and examples of which include $-[NH\text{-}CHR')_p\text{-}CO]_n-$ wherein R' is side chain of an amino acid, n is an integer 1 to 10; hydroxy acids; diols; aminothiols; etc., [0052]. This reads on instant claims 7 and 8. Hence Leung anticipates instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 10 and 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leung (US 2002/0169125 A1) as applied to claims 7 and 8 above, in view of Greenwald, 2001, Journal of Controlled Release, 74, 159-171 and further in view of Duncan, 2001, Journal of Controlled Release, 74, 135-146.

Leung discloses a polyanionic polymer conjugated to a drug. The drug being selected from the group that consisted of tubulysin, dolastatin (psuedopeptides) which exhibits cytotoxic properties ([0012] and claim 45). Leung also discloses that the drug can be conjugated to the polyanionic polymer through an indirect linkage (linker) such as a bifunctional spacer [0051] and examples of which include $-[NH\text{-}CHR')_p\text{-}CO]_n$- wherein R' is side chain of an amino acid, n is an integer 1 to 10; hydroxy acids; diols; aminothiols; etc., [0052]. This reads on instant claims 7

and 8. Since the linker used in the conjugation use diol and $-[NH-CHR')_p-CO]_n-$ linkers that conjugate the drug and the polymer, it reads on the instant claims 14-20 that recites the variable 'V' being an oxygen atom, or -NH or $-O-(CR^aR^b)_n-O-$ which belongs to the genus of diols.

Leung discloses a conjugate of tubulysin (a cytotoxic agent), a linker and a polyanionic polymer, it does not disclose Polyethylene glycol as the polymer.

Greenwald discloses PEG drug conjugates and states that no low molecular weight (<20,000 d) PEG drug conjugates have led to a clinically approved product (abstract). It further states that a renaissance has taken place in the field of higher molecular weight (>20,000 d) conjugates of anticancer drug conjugates and especially employing PEG (40,000 d). This change in the use of higher molecular weight of PEG has improved the plasma circulating half life to 8-9 h in the mouse (abstract). The range in the molecular weight of PEG used, i.e., between 20,000 and 40,000 d for the conjugation to anticancer drugs in Greenwald reference reads on the instant claims 10, 21 and 22.

Greenwald further discloses that "successful application of the PEG prodrug (40,000 d) concept to anticancer agents and the initiation of a clinical trial of PEG-camptothecin by Enzon may be viewed as the beginning of a drug delivery methodology which can be extended to many other classes of compounds: cytokines, blood factors, peptides, antifungals, antibiotics, and immunosuppressive agents, to mention a few".

Duncan discloses that conjugation of anti-tumor dugs to hydrophilic polymers provide an opportunity to solubilize poorly water soluble drugs, Improve tumor targeting and reduce drug toxicity (Background). Duncan reiterates that the optimum molecular weight of the polymer for conjugation that allows renal elimination is less than 30-40 kDa (Section 2.1 on page 138).

Duncan also discloses several polymer conjugated drugs, for example polyglutamic acid-paclitaxel which is a polyanionic polymer conjugated drug (as also disclosed by Leung) in phase I/II testing. Instant claim 7 is drawn to a polymer conjugated tubulysin and instant claim 12 and 13 are drawn to method of treating patient suffering cancer. Since Duncan discloses polyanionic conjugated drug in the clinical trials, it reads on the instant claims 12 and 13.

It would have obvious to one of ordinary skill in the art to combine the afore-discussed teachings of Leung, Greenwald and Duncan to arrive at the instant invention. It would have been obvious because, the problem that is solved by the instant invention is the conjugation of tubulysin with a polymer using a linker molecule. This aspect of the invention was well recognized in the Leung and the reference discloses such a conjugate of tubulysin with polyanionic polymer. Duncan teaches that polyanionic conjugated paclitaxel in clinical trials and Greenwald discloses that anticancer drugs conjugated to higher molecular weight PEG extends half life in plasma. Although the cited references do not teach the conjugation of tubulysin with PEG, the motivation to do so comes from Greenwald. Greenwald as mentioned earlier further states that "successful application of the PEG prodrug (40,000 d) concept to anticancer agents and the initiation of a clinical trial of PEG-camptothecin by Enzon may be viewed as the beginning of a drug delivery methodology which can be extended to many other classes of compounds: cytokines, blood factors, peptides, antifungals, antibiotics, and immunosuppressive agents, to mention a few". This would be a strong motivation for one of ordinary skill in the art to conjugate the tubulysin to PEG to increase the half-life in plasma and lower the toxicity as taught by Duncan and Greenwald. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the

teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

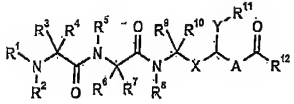
Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 7 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-32 of copending Application No. 10520793 in view of Leung (US 2002/0169125 A1). Instant claim 7 is drawn to a compound of formula U-V-W wherein U is represented by the formula,



(I)

wherein, V is a linker and W is a polymer.

Claim 19-32 of the copending Application No. 10520793 recites compound of formula I shown above.

The invention in copending application 10520793 does not disclose a conjugate U-V-W wherein the variable 'U' is the compound of formula I.

However, Leung discloses a polyanionic polymer conjugated to a drug. The drug being selected from the group that consisted of tubulysin, dolastatin (psuedopeptides) which exhibits cytotoxic properties ([0012] and claim 45). Leung also discloses that the drug can be conjugated to the polyanionic polymer through an indirect linkage (linker) such as a bifunctional spacer [0051].

One of ordinary skill in the art would combine the teachings of the copending Application No. 10520793 with Leung to arrive at the instant invention. Because, Leung teaches conjugation of tubulysin a species of formula I of instant application with a polyanionic polymer via a linker. One would be motivated to do so given the fact that copending application teaches the generic formula of compound I and Leung discloses a conjugate of a species of formula I

with a polymer using a linker. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

Claim 7 directed to an invention not patentably distinct from claims 19-32 of commonly assigned 10520793. Specifically, as illustrated above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned instant application and 10520793, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c),

either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654